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Blood Cadmium Concentrations in the General Population of British Middle-aged Men

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Blood cadmium concentrations were determined for 6919 men aged 40–59 randomly selected from general practice registers in 24 British towns. The mean and median blood cadmium were 1.9 and 1.4 μg/l respectively and the distribution was highly skewed. The mean levels in non-smokers was 1.0 μg/l and current smokers showed a marked gradient with the daily amount smoked, with a mean of 3.9 μg/l in men smoking 40 or more cigarettes per day. Whereas 95% of men who never smoked had blood cadmium < 2.0 μg/l, 80% of men smoking 20 or more cigarettes a day exceeded this figure. 1% of the men had blood cadmium concentrations ≥ 7 μg/l virtually all of whom currently smoked cigarettes. Blood cadmium levels in ex-smokers were much lower than in current smokers even for those who had stopped within the past year. However, the mean levels in ex-smokers remained higher than the 'never smoked' for several years after stopping. There was little evidence that age, social class, or alcohol consumption were associated with blood cadmium levels after allowance for cigarette smoking.

There is substantial geographic variation in mean blood cadmium for middle-aged men which could not be completely accounted for by smoking differences. Towns in the south and east of England all had mean levels under 2.0 μg/l whereas the majority of towns in other parts of Britain had mean levels greater than 2.0 μg/l. Possible reasons for this geographic pattern (e.g. geochemistry, industrial exposure, dietary differences) need further exploration.

Introduction

Increased industrial use of cadmium and environmental pollution with cadmium-related waste products has provoked an appropriate concern about the potential health consequences of human exposure to this highly toxic metal. There have been many studies of occupationally exposed workers but little information on the exposure to cadmium of the general population of Great Britain. Two useful contributions include a study of cadmium concentrations in nearly 1000 human kidneys obtained at autopsy[1] and a survey of cadmium in foods[2].

This paper describes the findings of a large-scale survey of blood cadmium levels in British middle-aged men. They provide a valuable insight into the sources and potential health consequences of low level cadmium exposure. The principal issues discussed are the role of cigarette smoking and the geographic variation in blood cadmium concentrations.

Methods

During 1978 to 1980, the British Regional Heart Study examined 7735 men aged 40–59 selected from the age-sex registers of representative general practices in 24 British towns. The criteria for selecting the towns, general practices, and subjects as well as the methods of data collection are reported elsewhere.[3] The 24 towns had populations of 50 000 to 125 000 and were chosen to include all geographic regions. The general practice in each town had a social class distribution representative of the town. The men were selected at random from age-sex registers and there was a 78% response rate.

Blood cadmium analyses were carried out on 6919 men (89%) from frozen whole blood samples by electrothermal atomization and atomic absorption spectrophotometry.[4] Internal quality control of blood cadmium analyses was maintained by analysing singly, portions of two control blood specimens before and

after every set of five survey samples which were analysed in duplicate. The concentrations of cadmium and the limits of acceptance for these specimens were 0.9 ± 0.5 μg/l and 6.0 ± 0.5 μg/l respectively. During the 3-year period of the study three different analysts were employed for the cadmium measurements. The absence of inter-operator bias and the temporal stability of the analytical method and of the blood specimens was demonstrated by duplicate analyses by two operators of selected batches of survey specimens. In two such exercises, based on 111 and 63 samples, the mean differences between operators were 0.004 and 0.035 μg/l respectively (Table 1), both of which are negligible in comparison with the observed blood cadmium levels for the survey specimens. The accuracy of the blood cadmium method was indicated by the good analytical performance in the United Kingdom External Quality Assessment Scheme (Figure 1).

Cigarette smoking habits were recorded using a standardized questionnaire. Men were classified into 8 smoking categories: never smoked, ex-cigarette smokers, pipe and cigar smokers who never smoked cigarettes, pipe and cigar smokers who are ex-cigarette smokers, and current cigarette smokers at 4 levels (1–19, 20, 21–39 and ≥ 40 per day). For ex-cigarette smokers the number of years since stopping was also recorded.

Alcohol consumption was also recorded using a standard questionnaire based on the frequency, amount and type of alcohol usually consumed. Men were classified into 6 social classes according to their longest held occupation.

Three tap water samples (first draw, random daytime and flushed) were collected from the homes of each of about 40 men per town. Cadmium was among the trace elements determined in these samples using inductively-coupled plasma-emission spectrometry,[5] along with water hardness and several other water parameters.[6]

Results

Overall distribution

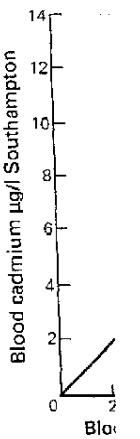
Figure 2 shows the distribution of blood cadmium concentrations for all 6919 men. The distribution is skewed with a mean of 1.94 μg/l and median 1.4 μg/l. 68 men (1%) had blood cadmium ≥ 7 μg/l and the highest recorded value was 19.0 μg/l.

Smoking habits

Figure 3 shows the mean blood cadmium concentrations for men classified by their current and previous smoking habits. 1469 men who had never smoked had a mean blood cadmium of 0.91 μg/l. Current cigarette smoking produced a marked dose–response relationship with blood cadmium levels, with a mean blood cadmium of 3.34 μg/l for men smoking 20 cigarettes per day and a mean of 3.88 μg/l for men smoking 40 or more cigarettes per day. Pipe and cigar smokers had intermediate values of mean blood cadmium, 1.32 μg/l

Table 1 Repeated analyses of blood specimens for cadmium to demonstrate comparability of data obtained by different analysts and temporal stability of the method

	Analyst A	*Analyst B*	*Analyst B*	*Analyst C*
Date of analyses	June 1982	Feb 1984	July 1984	Aug 1985
Number of blood samples from at least two survey areas	111	111	63	63
Observed concentration ranges of Cd (μg/l)	0.4–6.5	0.2–7.9	0.2–5.5	0.3–5.6
Mean blood Cd (μg/l)	2.197	2.194	1.921	1.886
Difference in means (μg/l)	+0.004		+0.035	
Mean difference (μg/l) regardless of sign	0.406		0.324	
Range of differences in blood Cd concentrations (μg/l)	−2.6 to +1.9		−0.9 to +2.1	
Percentage of results with differences:				
≤ 0.2 μg/l	50		51	
≤ 0.5 μg/l	74		83	
≤ 1.0 μg/l	90		98	



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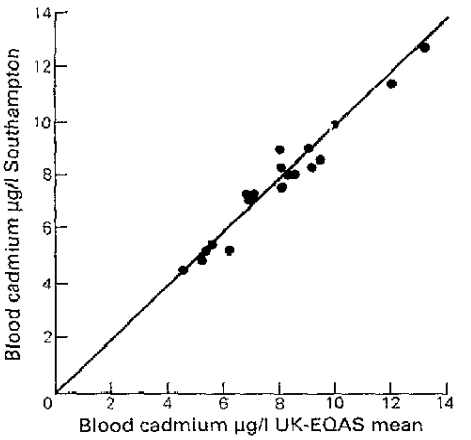
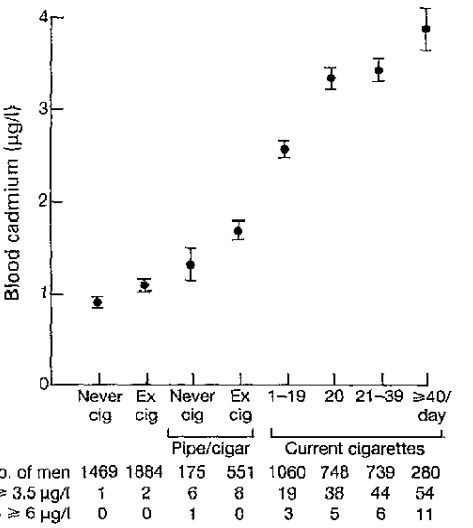


Figure 1 Performance of Southampton laboratory in UK External Quality Assessment Scheme.

for those pipe and cigar smokers who had never smoked cigarettes. The large group of ex-cigarette smokers had a mean blood cadmium of 1.10 µg/l which although only 21% higher than for those who never smoked is still a highly significant increase.

A blood cadmium level of 3.5 µg/l was exceeded by 1% of men who never smoked compared with over 40% of men who smoke 20 cigarettes or more per day. Blood cadmium levels over 6 µg/l were almost entirely confined to current smokers and 11% of



No. of men	1469	1884	175	551	1060	748	739	280
% ≥ 3.5 µg/l	1	2	6	8	19	38	44	54
% ≥ 6 µg/l	0	0	1	0	3	5	6	11

Figure 3 Mean blood cadmium concentrations (and 95% confidence intervals) for men in 8 smoking categories.

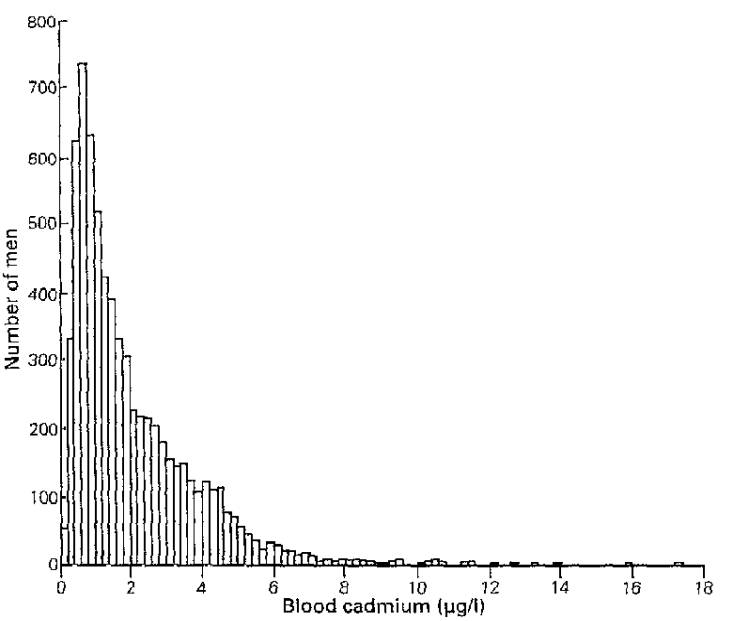


Figure 2 Distribution of blood cadmium concentrations in 6919 British men aged 40–59 years.

heavy smokers (≥ 40 cigarettes per day) had blood cadmium ≥ 6 μg/l.

The extremely strong relationship between cigarette smoking and blood cadmium is further illustrated in Figure 4 which compares the frequency distribution of blood cadmium for the never smoked (n = 1469 men) and men who currently smoke 20 or more cigarettes daily (n = 1767 men). It can be seen that there is only slight overlap between the two distributions with 86% of the never-smoked having blood cadmium < 1.5 μg/l compared with only 7% of men smoking ≥ 20 cigarettes.

Figure 5 shows the mean blood cadmium levels for the 1884 ex-smokers grouped according to the estimated number of years since stopping smoking. Even for men who stopped in the last year or two there is a considerable decrease in blood cadmium compared with current smokers. Nevertheless, blood cadmium levels remain slightly elevated compared with the never-smoked for many years after stopping, so that only after 10 years abstinence from smoking do we see a mean blood cadmium level similar to that of men who never smoked cigarettes.

Geographic variation

The mean blood cadmium levels for men in each town are presented in Figure 6. For all towns (except Scunthorpe) the means are based on over 200 men and each standard error of the mean is less than 0.12 μg/l. In Scunthorpe, only 102 men were included due to problems encountered in the laboratory with some of the specimens, so the standard error of the mean for Scunthorpe = 0.18 μg/l. There is a marked geographic variation in blood cadmium. All towns in the south and east of England have mean blood cadmium levels < 2.0 μg/l whereas the majority of other towns (11 out of 17) have mean levels > 2.0 μg/l.

It is important to note that the prevalence of cigarette smoking varies markedly between towns with generally lower smoking rates in the south and east of England.[7] To allow for this, Figure 6 also shows the town means of blood cadmium for those men not currently smoking cigarettes, pipe or cigars. The number of men per town is consequently reduced, but only in two towns, Scunthorpe (45) and Grimsby (95) were there fewer than 100 men. Evidently, much of the geographic variation in blood cadmium is attributable to smoking. For instance, the men surveyed in Grimsby had the highest proportion of cigarette smokers of all the towns and therefore they showed an elevated mean blood cadmium. However, the 95 non-smokers in Grimsby had a mean blood

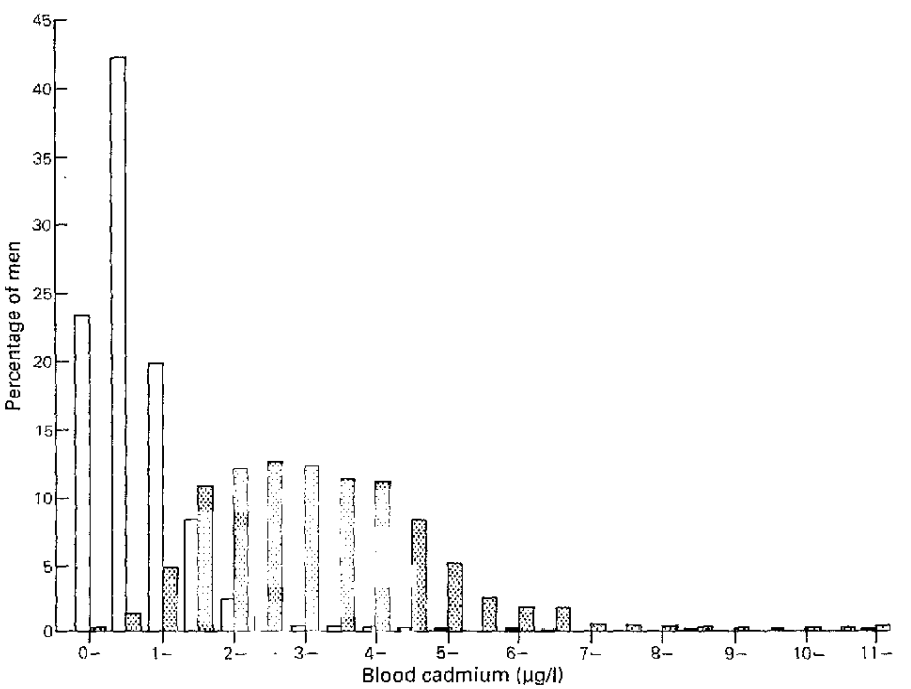


Figure 4 The percentage distributions of blood cadmium for men who never smoked (n = 1469) and men who currently smoke 20 or more cigarettes daily (n = 1767). □, never smoked; ▨, currently smoke ≥ 20 cigarettes per day.

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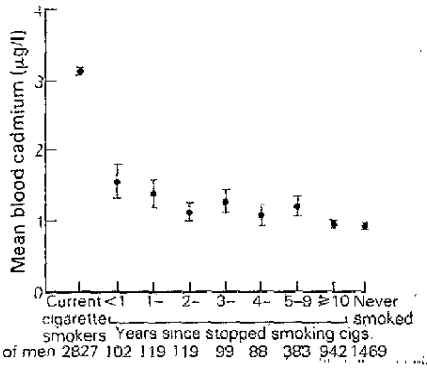

Figure 5 Mean blood cadmium concentrations (and 95% confidence intervals) for ex-cigarette smokers according to the number of years since stopping smoking.

cadmium near to the overall mean for non-smokers. In non-smokers, mean blood cadmiums appear highest in three towns in the North West (Shrewsbury, Southport and Wigan) whereas Guildford had an exceptionally low mean blood cadmium.

Age, alcohol and social class

Table 2 shows the mean blood cadmium levels for men categorized according to age, alcohol consumption and social class. Since smoking habits have such a marked effect on blood cadmium, Table 2 also shows these mean blood cadmiums adjusted for smoking habits (using an analysis of covariance technique).

Unadjusted for smoking, there appears to be a substantial association between alcohol consumption and blood cadmium, with higher mean concentrations in the heavier drinkers (> 6 drinks, daily or at weekends). However, alcohol consumption and smoking habits are strongly related, with heavy drinkers having a higher proportion smoking cigarettes.[7] After adjustment for smoking differences there is no discernable relationship between alcohol consumption and blood cadmium levels.

Men in the manual social classes have higher mean blood cadmiums but this is primarily due to the fact that they smoke much more than the non-manual classes.[7,8] Hence, adjustment for smoking differences greatly reduces the social class differences in mean blood cadmium. There remains a 7% excess in mean blood cadmium amongst manual workers which though small in magnitude is still statistically significant because of the large numbers of men.

There is no indication that blood cadmium levels increase with age. Indeed, after adjustment for smoking habits there is a slight decline in mean blood cadmium in the older men.

Discussion

This study provides more extensive information on blood cadmium concentrations in the general population of middle-aged British men than has previously been available. Random selection of men from the age-sex registers of group general practices ensures a reasonably representative sample. Also, the laboratory's participation in internal and external quality control schemes has ensured that the data on blood cadmium concentrations can be interpreted reliably.

Smoking habits

The most striking feature is the extraordinarily strong relationship between cigarette smoking and blood cadmium concentrations. Current cigarette smokers have a mean concentration over three times higher than non-smokers (Figure 3) and there was little overlap in the blood cadmium distributions of the never-smoked and those smoking 20 or more cigarettes per day (Figure 4). It is clear that amongst smokers the principal source of exposure to cadmium is from cigarettes. A previous report on these same men[9] has also shown blood lead to be related to cigarette smoking but that relationship, though of some importance, is much weaker than the present cadmium-cigarette relationship. Other international surveys of blood cadmium in the general community[10–12] and studies of occupationally exposed workers[13,14] have also found strong smoking relationships though the larger number of subjects in this present study provide a more precise definition of the association.

Amongst the 1469 men who had never smoked the median blood cadmium concentration was 0.7 µg/l, 5% exceeded 2.0 µg/l of whom 1% exceeded 3.9 µg/l. By comparison, the 2827 current cigarette smokers had a median concentration of 2.8 µg/l, 5% exceeded 6.0 µg/l of whom 1% exceeded 8.5 µg/l. These figures should be of value in defining reference levels and upper limits of 'normality' for smokers and non-smokers.

Blood cadmium concentrations in our British men appear considerably higher than in a study of 473 Swedish men both for smokers and non-smokers,[11] median concentrations being 0.2 and 1.4 µg/l respectively. A more extensive study obtained blood cadmium concentrations in 1823 teachers in 10 countries, (Belgium, China, India, Israel, Japan, Mexico, Peru, Sweden, USA and Yugoslavia).[10] Amongst smokers the male median blood cadmium levels were generally lower than in our British men, except in Mexico and Yugoslavia. Amongst non-smokers median levels were more comparable with our British findings. This suggests the possibility that the cadmium content of British manufactured cigarettes may be somewhat higher than in other countries. Alternatively, teachers may be too narrow a social group for comparison with our general population, or British smokers may have

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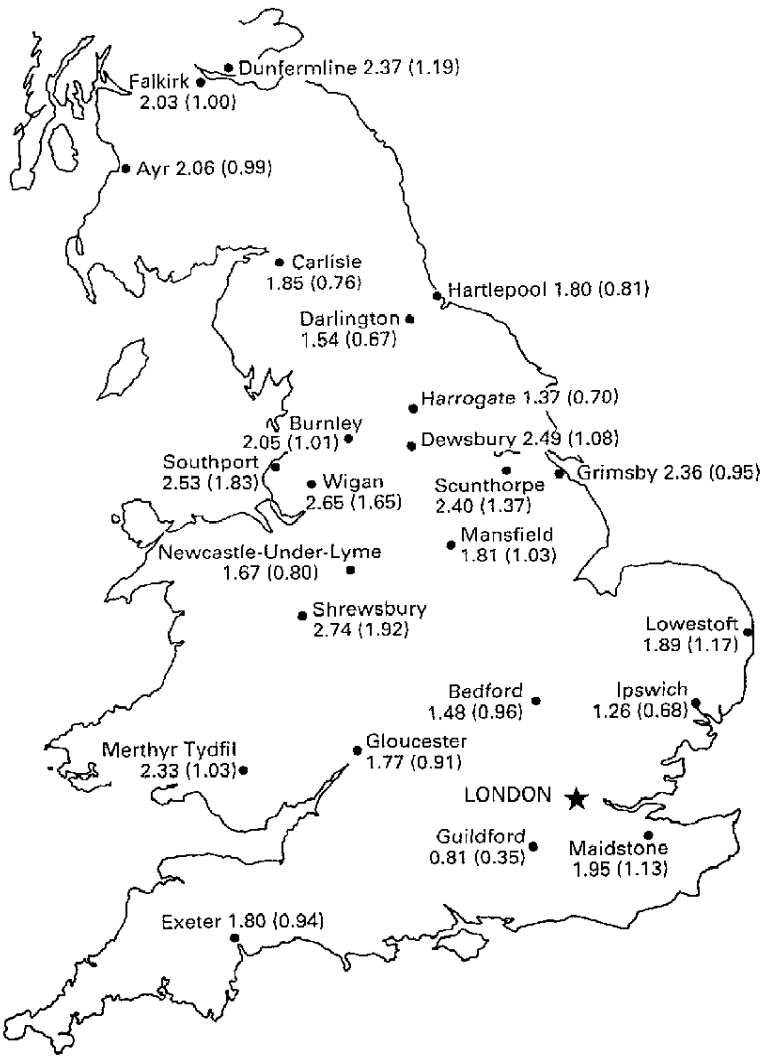

Figure 6 Mean blood cadmium concentrations (μg/l) in 24 towns, for all men and also for current non-smokers (in parentheses).

a higher mean number of cigarettes per day, or technical differences may exist between studies.

Decline after stopping smoking

It is generally recognized that blood cadmium concentrations indicate current rather than past exposure to cadmium. Hence it is valuable to study the decline in blood cadmium concentrations over time in any group whose principal source of exposure is removed. In Britain there has been a considerable reduction in cigarette smoking over the past 30 years and this study has 1884 ex-smokers for whom the number of years since stopping smoking was recorded. The rapid decline in blood cadmium amongst ex-smokers as compared with current smokers (Figure 5) is consistent with the concept that blood cadmium reflects recent exposure. However, one would then have expected the mean levels of ex-smokers after a year or two to be the same as for those who never smoked, whereas convergence only took place after ten years abstinence

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Table 2 Mean blood cadmium concentrations according to age, alcohol consumption and social class, both unadjusted and after adjustment for smoking habits

	No. of men	*Mean blood cadmium (μg/l)* Unadjusted	Adjusted for smoking habits
Age			
< 45	1660	1.90	1.99
45–49	1686	1.94	1.94
50–54	1763	2.01	1.93
≥ 55	1810	1.90	1.91
Alcohol consumption			
None	409	1.70	1.76
Occasional	1639	1.87	2.00
Weekends			
1–2	660	1.62	1.98
3–6	1073	1.97	1.87
>6 drinks*	992	2.24	2.01
Daily			
1–2	526	1.37	1.99
3–6	847	2.03	1.91
> 6 drinks*	769	2.37	1.87
Social class			
I Professional	559	1.39	1.85
II Intermediate	1561	1.66	1.86
III Non-manual (clerical)	659	1.76	1.87
III Manual (skilled)	2942	2.12	2.00
IV Semi-skilled manual	713	2.17	1.99
V Unskilled manual	266	2.22	1.97

* A drink = ½ pint of beer, a glass of wine or a single of spirits

from cigarettes. This would indicate that, although blood cadmium is primarily reflecting recent exposure, it may also be contributed to in part from the longer term accumulated body burden of cadmium. Thus, an elevated burden of cadmium in the kidney cortex as a result of many years of smoking cigarettes could lead to a residual small elevation in blood cadmium long after exposure to cigarettes has stopped.

One can postulate a two compartment model, whereby cadmium excretion in excess of that in men who never smoked is considered as two exponential decays, i.e. blood cadmium concentration in an ex-smoker = $A_1 e^{-k_1 t} + A_2 e^{-k_2 t}$ where t is the time since stopping smoking. The first component refers to removal of the direct exposure to cigarettes and has a relatively short half-life of less than six months. The second component refers to excretion back into the blood of excess cadmium in other organs (mainly the kidney) and from a plot of log (mean blood cadmium) against time since stopping in our ex-smokers this has an estimated half-life = log (½)/k_2 = 16 years. This is reasonably consistent with the view that excretion half-life of cadmium from the kidney is about 30 years.[11]

Also, such excretion from the kidney may arise because of tissue breakdown occurring with age[15] since cadmium levels in the kidney begin to decrease after the age of 50 to 60 years.[1,16] Our findings are also broadly comparable to the time trends in a small group of cadmium workers whose occupational exposure to cadmium had ceased.[17]

Alcohol consumption

The lack of association between alcohol consumption and blood cadmium concentrations after allowance for cigarette smoking is in agreement with previous research.[11,18] It is interesting to note that failure to take account of cigarette smoking would have given a false impression that heavy drinking was linked to a higher mean blood cadmium, since heavy drinkers are more likely to smoke cigarettes. This illustrates the principle that smoking habits must be allowed for in any study of cadmium exposure, whether it be into other sources or potential health consequences.

Social class

Similarly, the social class gradient in blood cadmium was largely attributable to social class differences in smoking habits. However, there remained a slight elevation in mean blood cadmium amongst manual workers after allowance for smoking which may indicate a degree of occupational exposure. This is to be investigated further by assessing the extent to which men with very high blood cadmiums (i.e. ≥ 4 μg/l in

non-smokers or ≥ 8.5 μg/l in current smokers) have occupations which are cadmium-related.

Geographic variation

We have shown evidence of substantial geographic variations in mean blood cadmium for British middle-aged men which can be partially attributed to the geographic differences in smoking habits. However, for current non-smokers there remain substantial and highly significant geographic differences in mean blood cadmium: 19 out of 24 towns have means in the range of 0.6–1.2 μg/l, three towns in the North and West (Shrewsbury, Southport and Wigan) have the highest means (1.92, 1.83 and 1.65 μg/l respectively) while Guildford has a much lower mean of 0.35 μg/l. Only in Guildford were the blood cadmium levels comparable to those found in Swedish men.[11]

At present there is no clear explanation as to why such geographic differences exist within Britain. Whereas geographic variations in blood lead could be partly attributed to lead in drinking water and an inverse association with water hardness,[19] water quality appears to have little connection with blood cadmium levels. Tap water samples from 40 households in each town revealed that water cadmium concentrations were mostly below the limit of detection (1.0 μg/l), and the highest mean water cadmium level was 2.0 μg/l in Lowestoft. There was no statistical association between the towns' mean blood cadmium (adjusted for smoking) and mean water cadmium or water hardness concentrations.

Experience in Shipham[20,21] indicates that a very high soil concentration of cadmium can result in moderately elevated body burdens of cadmium but there is no evidence that this could explain our between-town variation in blood cadmium. Also, industrial pollution and occupational exposure[13,14] can increase the body burden of cadmium but we are unaware at present of any industrial sources in our 24 towns. It is well recognized that the principal source of cadmium in non-smokers is from food,[2,22] particularly cereals and vegetables. It may be that dietary factors play some role in determining the observed town differences in blood cadmium and further research is underway to investigate this possibility.

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